REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1, 3, 5, 7, 9-14, and 17-18 presently appear in this application, with claims 13 and 14 being withdrawn, and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1, 3, 5, 7, and 9-12 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by adopting the recitation suggested by the examiner.

Claims 9-12 and 16 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Pecceu et al., Gene 97:253-258 (1991), and Bjorkdahl et al., Cancer Immunol. Immunother. 44:273-281 (1997), in view of Muzio et al. (actually Colotta et al.), WO 9612022, as set forth in previous Office Actions.

This rejection is obviated by the cancellation of claim 16 and the amendment to claim 9 to replace the product by process recitation with the positive recitation that the N-terminus of icIL-1ra-II begins at amino acid residue position +2 from the deduced start of translation on the icIL-1ra-II coding sequence and has the amino acid sequence of SEQ ID NO:11 at the N-terminus.

Claims 1, 3, 5, 7, 9-12, and 16 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Pecceu et al. and Selden et al., U.S. Patent 6,083,725 in view of Muzio et al. (actually Colotta et al., WO 9612022). This rejection is respectfully traversed.

Applicants restate part of the argument presented in the amendment of October 27, 2003, as follows:

At the time of filing the application, it was known in the art that the cleavage of the signal peptide and protein secretion not only depends on the sequence of the signal peptide itself, but also depends on the residues +1 and +2 of the protein of interest (see von Heijn, Nucl. Acids. Res. 1986 reference attached to the amendment filed October 27, 2003). For example, correct cleavage at residue +1A in Il-1 is predicted to occur if the growth hormone signal peptide (GHsp) is fused to the mature IL-1. In contrast, non-homogenous cleavage (at 3 different sites at residues +1M (15%), +3L (25%) and +5D (55%)) resulting in a non-homogeneous protein preparation is predicted using the same GH signal peptide with mature icIL-1ra-II. Moreover, the substitution of the insulin signal peptide for GHsp in both proteins results in essentially the same prediction, i.e., the homogeneous cleavage at residue +1A in IL-1, and non-homogenous cleavage in icIL-1ra-II.

Applicants have unexpectedly found that by fusing the sequence of icIL-1ra-II to the genomic growth hormone signal peptide, a secreted fully glycosylated active protein starting at amino acid +2A is obtained (Example 10, page 17). Such an unexpected result, in which the icIL-1ra-II protein starts at +2A instead of the predicted mixture of proteins starting at of +1M, +3L and +5D, as discussed above, was obtained because, in contrast to the cited and applied references, the DNA encoding the growth hormone signal peptide used in the expression vector is genomic and therefore contains the sequence of the first intron of the human growth hormone gene.

There is simply no disclosure, suggestion or motivation anywhere in the cited and applied references to use any vector for producing a specific icIL-1ra-II protein beginning with the amino acid residue position +2 from the deduced start of translation. For example, Pecceu did not analyze the N-terminal sequence of IL-1β produced with the vector comprising the hGH signal peptide, whereas Selden shows that the N-terminal processing of galA matched the N-terminal sequence predicted for the secreted protein (+1) (Column 14, lines 6-28). Muzio et al. (which is actually Colotta et al) teach a method for producing the recombinant icIL-1ra-II protein beginning at amino acid position +1 from the deduced start of translation (SEQ ID NO:14) and not at amino acid position +2. In fact, the use of the human

growth hormone signal peptide for secreting icIL-1ra-II predicts cleavage at 3 sites from the deducted start of translation of the gene: +1M, +3L and +5D, but not +2A, as discussed above. Accordingly, Pecceu, Selden and Muzio (Colotta) cannot be combined to arrive at the unexpected icIL-1ra-II protein of the present invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By _____
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\I\intp\AMITAI1\PTO\amd OA 1-5-04.doc